From Tc\textsuperscript{VII} to Tc\textsuperscript{I}; facile syntheses of bis-arene complexes \([^{99(\text{m})}\text{Tc}(\text{arene})_2]^+\) from pertechnetate\(^+\)

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Bis-arene complexes of technetium represent a fundamental class of organometallic compounds. Due to complex synthetic routes, no detailed insights into their properties have been reported so far. Reacting \([^{99}\text{TcO}_4]^-\) with arenes in the exclusive presence of AlCl\(_3\) gives highly stable \([^{99}\text{Tc}(\text{arene})]^{+}\) in good yields. These complexes have extraordinarily high stabilities, where oxidation is found to occur at potentials higher than +1.3 V and reduction at potentials below −2 V vs. Fc/Fc\(^+\). The \(^{99}\text{m}\text{Tc}\) analogues are similarly synthesised by applying a novel ionic liquid extraction pathway. Complexes of \(^{99}\text{Tc}\) with suitably functionalized arenes will represent new building blocks for bioorganometallic pharmaceuticals in molecular imaging.

Introduction

The realm of organometallic chemistry emerges from a relatively small number of basic ligand types, CO and cyclopentadienyl being two of them. Aromatic hydrocarbons constitute a further fundamental class of ligands, being isoelectronic with \([\text{C}_5\text{H}_5]^-\) \([\text{Cp}^-]\) but providing a different hapticity and different coordinating properties. Whereas \text{Cp}^− is a ubiquitous ligand in organometallic chemistry, complexes with aromatic hydrocarbons \text{C}_n\text{H}_{n+2}\ are much less explored, likely due to synthetic challenges and lower thermodynamic or kinetic stabilities. Since arene ligands are uncharged, vacancies at the metal center are more easily generated by haptotropic shifts than with \text{Cp}. Binary arene complexes represent precursors for numerous reactions.\(^1\)\(^−\)\(^3\) After their discovery by Fischer and Hafner in 1955, a multitude of synthetic approaches were reported. A recent, excellent review comprehensively describes these synthetic strategies in detail.\(^4\) Of particular interest are syntheses starting from metal halides, in the absence or presence of reducing agents such as aluminum or zinc. Where metals such as Fe\(^{ll}\) or Ru\(^{ll}\) are already present in the desired oxidation state, no reducing agents are needed; higher starting oxidation states require reduction for coordination to the arenes.\(^5\)\(^,\)\(^6\)

Bis-arene complexes \([\text{Re}^+\text{[C}_6\text{H}_5\text{R}_6]_2]^+\) \((n=1−6)\) are known but have been rarely studied and not in great detail. The first bis-arene complex of \(^{99}\text{Tc}\) was prepared by a very uncommon method, namely by element transmutation from \((^{99}\text{Mo[arene]}_3)\) via \(\beta\)-decay \(^{99}\text{Mo}\rightarrow^{99}\text{mTc}\rightarrow^{99}\text{Tc}\), the latter resulting directly from weighable amounts of \(^{99}\text{TcCl}_4\) in the presence of Al\(^{ll}\) and AlCl\(_3\)\(^7\)\(^,\)\(^8\) in low yields.\(^9\) Only recently, Kudinov and coworkers reported an improved synthesis of \([\text{Re}(\text{arene})_2]^{+}\) in moderate yields directly from \(\text{K}[\text{ReO}_4]\) with Zn\(^{0}\) as the reductant, AlCl\(_3\) as a Lewis acid and the arene as solvent.\(^10\) For over 50 years, no progress was made in the study of \([^{99}\text{Tc}[\text{C}_6\text{H}_5\text{R}_6]_2]^{+}\) type compounds, not only due to the radioactivity of this element but also because of synthetic difficulties. The preparation of binary halides such as \(^{99}\text{TcCl}_4\) as starting materials for accessing bis-arene complexes has made a significant impact over the past couple of years.\(^11\)\(^−\)\(^13\) Their syntheses are well described but their preparation and isolation are still not routine. A direct, high yield route to \([^{99}\text{Tc}(\text{arene})]^{+}\) complexes from \([^{99}\text{TcO}_4]^-\) salts would therefore be highly desirable since it would allow for the chemical exploration of these fundamental complexes and for classifying their properties in relation to neighboring elements. In addition, arene complexes with metastable \(^{99}\text{mTc}\) are potential molecular imaging agents: phenyl groups are frequent in pharmaceuticals and coordination of a \(^{99}\text{mTc}\) fragment to such arenes enables labeling without additional, pendent ligands,\(^14\) a concept verified with the \{\text{Cr}[\text{CO}_3]\}_2^−\) moiety bound to e.g. a phenyl ring in estradiol.\(^15\)\(^,\)\(^16\) The importance of the \{\text{M}[\text{arene}]\}_2^+\) moiety is corroborated by the impact of the \{\text{Ru}[\text{cymantrrene}]\}_2^+\) fragment in medicinal inorganic chemistry.\(^17\)\(^−\)\(^18\) Among their endeavors for new myocardial imaging agents, Wester et al. reported the synthesis of \([^{99}\text{mTc}[\text{arene}]_2]^{+}\) complexes in the early nineties. However, since the yields were “variable”, the syntheses were multi-step, and the pharmacology was not satisfactory, the compounds were not studied any further.\(^19\) Enthusiastic about new \(^{99}\text{Tc}\) chemistry and convinced that the application of
[¹⁹⁹Tc(arene)]₂⁺ complexes will extend beyond myocardial imaging, we developed practical, one step syntheses of [¹⁹⁹mTc(arene)]₂⁺ complexes in high yields and radiochemical purities, working towards a deeper understanding of the chemical and reactive properties of fundamental [¹⁹⁹Tc(arene)]₂⁺ complexes.

Results and discussion

The reaction of NH₄[¹⁹⁹TcO₄]²⁻, Zn⁰ and AlCl₃ gave yields of <15% when applying reaction conditions analogous to those described for rhenium by Kudinov et al. The products were difficult to separate from a black, colloidal material (ESI, Section 1†). In contrast to classical Fischer–Hafner conditions, we carried out the reaction without Zn⁰, assuming that Zn⁰ could over-reduce the starting material to metallic, colloidal Tc⁰. Addition of toluene to solid AlCl₃ and K[¹⁹⁹TcO₄] immediately produced a brown suspension. Heating the reaction mixture to 85 °C for 4 h gave a dark colored suspension. After extraction with water and precipitation with NH₄PF₆, we obtained [¹⁹⁹Tc(C₆H₆)₂]⁺ as [2]PF₆ in 75% isolated yield (Scheme 1). Comparable yields were obtained with mesitylene [NBu₄][¹⁹⁹TcOCl₄] and with no arene present, a yellow precipitate formed from a blue solution. Evaporation of the solvent and crystallization of the crude solid under N₂ in dimethylformamide (DMF) gave large yellow crystals. From X-ray analysis the intermediate was confirmed to be [Al(DMF)₆][¹⁹⁹TcCl₆]Cl·DMF. The presence of this Tc⁴⁺ complex supports the role of AlCl₃ as a reducing agent of Tc⁷⁺ or Tc⁵⁺ to form Tc⁴⁺. Consequently, the reaction to afford [¹⁹⁹Tc(arene)]₂⁺ complexes can also be performed from K[¹⁹⁹TcCl₆] with otherwise identical conditions as those from K[¹⁹⁹TcO₄] (ESI, Section 1†). The complexes [2]PF₆ and [4]PF₆ were prepared by this route in good yields.

These reactions represent a new procedure towards bis-arene complexes of group 7 elements. They combine pure arene substitution with elements already present in the desired oxidation state with concerted reduction–coordination, but without additional reductants such as Zn⁰ or Al⁰. Only one similar process, for [Fe(C₆H₆)₃]⁷⁺, has been reported in the literature.²¹

The reaction of K[¹⁹⁹TcO₄] in benzene with AlCl₃ did not lead to [¹⁹⁹Tc(C₆H₆)₂]⁺ ([1]⁺). In this reaction, only unidentified products formed and ⁹⁹Tc NMR spectra gave no evidence for Tc⁴⁺ species. Significant amounts of [¹⁹⁹TcO₄]⁻ (~50%) could be recovered. We concluded that substituted alkenes with enhanced donating properties stabilised the intermediate oxidation states better than unsubstituted benzene. This interpretation is supported by the marked electrochemical differences found between the complexes (vide infra). Complex [1]PF₆ could be synthesized from [¹⁹⁹TcO₄]⁻ via the Fischer–Hafner route in moderate yields with Zn dust as a reductant. ²¹

⁹⁹Tc NMR spectroscopy provides valuable insights into the symmetry and electronic properties of technetium complexes.¹⁷,²² Tc¹⁺ signals are typically found between ~3000 and ~1000 ppm relative to [¹⁹⁹TcO₄]⁻ at 0 ppm.²² Due to a scalar coupling of the nuclear spin (I = ⁹/₂) to the quadrupole moment of the ⁹⁹Tc nucleus, decreasing symmetry of the complexes is accompanied by a strong line broadening. However, the presented [¹⁹⁹Tc(arene)]₂⁺ complexes have highly symmetrical first coordination spheres, reflected in their small half line widths (8–26 Hz). The observed ⁹⁹Tc NMR signals, [¹⁹⁹Tc(benzene)]²⁻ at ~1860 ppm (ν₁/₂ = 8 Hz), [¹⁹⁹Tc(toluene)]²⁻ at ~1744 ppm (ν₁/₂ = 26 Hz), [¹⁹⁹Tc(tetralin)]²⁻ at ~1586 ppm (ν₁/₂ = 11 Hz) and

Scheme 1 Reaction sequence for the preparation of [¹⁹⁹Tc(arene)]₂⁺ complexes.
[99Tc(mesitylene)₂]⁺ at −1532 ppm (δ₁₂ = 14 Hz), suggest that a higher substitution pattern at the aromatic backbone leads to a shift in the 99Tc resonance to lower field. The 99Tc NMR spectrum of [1] [PF₆] (including the side product [5] [PF₆]) is shown in Fig. 2. All 99Tc NMR spectra are given in Section 3 of the ESI. ³¹H NMR spectra show the strong influence of the metal center on the shift of the aromatic protons, which appear in the region around 5.5 ppm. Comparable features are found for isoelectronic complexes of the benzene complexes of RuII and Cr⁰, for which the arene signals are found at around 6.90 ppm and 4.21 ppm respectively.

The small but significant chemical shift differences in the 99Tc NMR spectra of the complexes are caused by the different numbers of groups with negative Hammett constants. Increased electron donation to the 99Tc center should be paralleled with corresponding electrochemical properties. Cyclic voltammetry (CV) investigations are in agreement with this prediction and reversible oxidation waves for the TcI/II couple were found at surprisingly high values, generally E¹/₂ > +1.4 V vs. Fe/Fe⁺ in acetonitrile (Fig. 3 and ESI, Section 5†). Along the series [1]⁺ → [4]⁺, the oxidation potentials become less positive with an increasing number of donors on the arenes. Irreversible and essentially arene independent reductions assigned to the 99Tc⁰⁺ couple appear below −2 V. As expected from general trends in the triads of the d-block elements, the rhenium homologues of [1]⁺ → [4]⁺ showed the Re⁰⁺ couples shifted by about 0.19–0.15 V towards more negative potentials as compared to the 99Tc compounds (see ESI, Table ESI5.1.1†), i.e. they are more easily oxidised than the 99Tc homologues, albeit still at considerably positive potentials. Comparing the herein reported 99Tc potentials with those of the neighbouring elements, for those which are available, confirms general trends for d-block elements in the periodic system. For instance, E¹/₂ for [Cr(C₆H₆)₂]⁺⁺ is reported at +0.82 V vs. Ag/AgCl, and hence, although to our knowledge unreported, the corresponding molybdenum complex should have an even more negatively shifted potential. For [Ru(C₆H₆)₂]²⁺/³⁺, no potentials for the Ru⁰/II couple are reported, probably because observation of the oxidation is not possible in common solvents. On the other hand, E¹/₂ for the Ru⁰/II couple is found at −1.02 V, almost 1 V more positive than the potential of its 99Tc analogue (Table ESI5.1.1†). Spectroelectrochemistry measurements in an OTTLE cell supported the reversibility of the [Re(arene)₂]/[Re(arene)₂]²⁺ couple. The Re³ complex is oxidised to Re⁴⁺ and reduced back to Re²⁺ as is evident from the isosbestic points detected in the electrochemical experiment (Fig. ESI5.10.1†). In agreement with these electrochemical potentials, the [99Tc(arene)]⁻ complexes are difficult to chemically oxidise and are very stable under ambient conditions. They are also insensitive to pH changes and do not decompose over the whole pH range even at elevated temperatures, an important feature for their potential application as molecular imaging agents.

The high yields and one step syntheses to [99Tc(arene)]⁻ complexes are the incentives for translating the reaction conditions to attain short-lived 99mTc complexes. Apart from fundamental interests, conjugation of biologically active groups to the arene ring will open a path to novel, functionalised and targeted SPECT imaging agents. In the original preparation of [99mTc(arene)]⁻ complexes, the multiple steps required for transferring [99mTcO₄]⁻ from the generator saline eluate into an organic solvent were difficult and time consuming, and ultimately prohibitive for any application. To facilitate this step, we coated a glass vial with a thin layer of ionic liquid (IL) by evaporating a dilute solution of [P(C₆H₁₃)₃(C₁₄H₂₉)]Br in MTBE. Addition of the generator eluate to this vial resulted in extraction of 80–97% of [99mTcO₄]⁻ into the IL layer within 10 min by an anion exchange process (Scheme 2). The saline was removed and the IL was dissolved in the corresponding arene and added to a vial charged with AlCl₃ under N₂. The vial was heated for 10 min at 100 °C in a microwave reactor. Upon addition of water, the [99mTc(arene)]⁻ complexes were extracted in yields of

**Scheme 2** Extraction of Na+[99mTcO₄]⁻ from saline (0.9% NaCl in H₂O) into an ionic liquid.
yield of the $[{^{99}\text{Tc}(\text{tetralin})_2}]^+$ complex was reduced due to
($[{^{99}\text{Tc}(\text{toluene})_2}]^+$: 0.45 min, $[{^{99}\text{Tc}(\text{mesitylene})_2}]^+$: 0.42 min,
shorter than that of the corresponding Re complex. This e
b
This time delay was quanti
constant time delay (here 0.5 min) from the UV signal (Re).

Assessment of the identities of the $^{99}\text{Tc}$ complexes by HPLC
co injection with fully characterised rhenium homologues and
subsequent comparison of retention times is an FDA accepted
procedure. Due to the serial arrangement of the UV- and radio-
detectors, the respective $\gamma$-signal ($^{99}\text{Tc}$) is separated by a
constant time delay (here 0.5 min) from the UV signal (Re). This
time delay was quantified with $[{^{99}\text{Tc}(\text{toluene})_2}]^+$ (UV- and
$\beta$-detection for the same compound, Fig. 4).

Despite their isoostructural nature and comparable physico-
chemical properties, slightly different retention times ($R_t$) ($\Delta R_t$
different from the 0.5 min) are sometimes observed for homologous
$^{99}\text{Tc}$ and Re complexes. This makes their iden-
tification by $R_t$ comparison somewhat ambiguous. The reported
$[{^{99}\text{Tc}(\text{arene})_2}]^+$ complexes provide good examples for this
ambiguity, where the $R_t$ for $[{^{99}\text{Tc}(\text{benzene})_2}]^+$ is 0.58 min
shorter than that of the corresponding Re complex. This effect
diminishes with the increasing number of arene substituents
$[{^{99}\text{Tc}(\text{toluene})_2}]^+$: 0.45 min, $[{^{99}\text{Tc}(\text{mesitylene})_2}]^+$: 0.42 min,
$[{^{99}\text{Tc}(\text{tetralin})_2}]^+$: 0.39 min). These small but non-negligible
uncertainties in the assessment of the identities of $^{99}\text{Tc}$
complexes can only be ruled out by HPLC co injection with fully
characterised $^{99}\text{Tc}$ analogues; $\Delta R_t$ must be approximately 0.5
min (for our instrumental arrangement). This has additionally
been verified by coinjection of $[{^{99m}\text{Tc}(\text{tetralin})_2}]^+$ and
$[{^{99m}\text{Tc}(\text{toluene})_2}]^+$; the separation of the UV signal ($^{99m}\text{Tc}$ complex
and the $\gamma$-signal ($^{99m}\text{Tc}$) showed the expected separation ($\Delta R_t = 0.51$
min, ESI, Section 2†). We emphasise that such direct
comparisons between $^{99m}\text{Tc}$ and $^{99}\text{Tc}$ complexes are very rarely
reported, if ever, but are ultimately the only way to truly assess
the identity of a $^{99m}\text{Tc}$ complex.

Conclusions
Mono- and bis-arene complexes of d-block elements are
fundamental in organometallic chemistry. The difficulty in
accessing such complexes, especially for technetium where
$[{^{99}\text{Tc}(\text{arene})_2}]^+$ type complexes have been essentially non-exist-
ten, has impeded their detailed chemical studies and their
application in molecular imaging. We now present a new, high
yielding synthetic procedure to afford these fundamental
organometallic complexes of the group 7 elements. In our
procedure no additional reducing agents are required, with the
exception of the synthesis of $[{^{99}\text{Tc}(\text{benzene})_2}]^+$. AlCl₃ serves as
an oxygen abstracting Lewis acid and at the same time as a
source of chloride reducing agent in the high valency regime.
The reaction procedure can be fully applied to $^{99m}\text{Tc}$, enabling
the introduction of novel organometallic complexes in the area
of molecular imaging. Studies with non-alkyl arene substituents
are currently ongoing.

Experimental section
General preparation of $[{^{99}\text{Tc}(\text{arene})_2}]^+$ complexes
Caution: $^{99}\text{Tc}$ is a weak $\beta^-$ emitter ($E_{\text{max}} = 0.292$ MeV, half life
time $= 2.12 \times 10^5$ y. It should be handled only in appropriately
equipped laboratories.

Method (a) NH₄[¹⁰⁹TcO₄] (18 mg, 0.10 mmol), Zn-dust (22 mg,
0.34 mmol), AlCl₃ (134 mg, 1.00 mmol) and the corresponding
arene (6 ml) were heated to 85 °C. After 8 h, the solvent of the
resulting dark brown suspension was removed with a stream of
N₂. The residue was washed with Et₂O (3 × 2 ml). The remaining
solid was extracted with H₂O (3 × 2 ml) and the aqueous
solution was filtered. NH₄PF₆ (150 mg, 0.92 mmol) in
H₂O (1 ml) was added to the red-brown filtrate. The colorless
precipitate was filtered off, washed with H₂O (2 × 0.5 ml) and
Et₂O (2 × 0.5 ml) and dried in vacuo to give $[{^{99}\text{Tc}(\text{arene})_2}][\text{PF}_6]$ as
a pale yellow powder. Alternatively, the precipitate can be
extracted with CH₂Cl₂ from the aqueous suspension.

Method (b) K[¹⁰⁹TcO₄] (20 mg, 0.10 mmol), AlCl₃ (200 mg,
1.50 mmol) and the corresponding arene (8 ml) were heated at
85 °C. After 4 h, H₂O (6 ml) was added to the hot dark brown
solution and the aqueous phase was separated and filtered.
The process was repeated with additional H₂O (2 × 2 ml). To
the combined aqueous solutions was added a solution of NH₄PF₆
(150 mg, 0.92 mmol) in H₂O (1 ml). The formed colorless
precipitate was filtered, washed with H₂O (2 × 0.5 ml) and dried
in vacuo to give $[{^{99}\text{Tc}(\text{arene})_2}][\text{PF}_6]$.

Method (c) K[¹⁰⁹TcCl₆] (37 mg, 0.10 mmol), AlCl₃ (134 mg,
1.00 mmol) and the corresponding arene (8 ml) were heated at
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85 °C for 4 h. H2O (4 ml) was added to the hot dark brown solution and the aqueous phase was separated and filtered. The process was repeated with additional H2O (2 × 2 ml) and to the combined aqueous solutions was added a solution of NH4PF6 (150 mg, 0.92 mmol) in H2O (1 ml). The colorless precipitate was filtered, washed with H2O (2 × 0.5 ml) and dried in vacuo to give [%99mTc(arene)2][PF6] as a pale yellow powder.

General preparation of [%99mTc(arene)2] complexes

The ionic liquid [P(C6H13)3(C14H29)]Br (2 mg) dissolved in 0.1 ml methyl tert-butyl ether (MTBE) was added to a capped vial. Under constant rotation of the vial, the solvent was evaporated by a N2 stream. The [%99mTcO4]− eluate (1–2 ml) was added and the vial was gently shaken for 10 min. The aqueous solution was removed and the vial was purged with N2 for 30 min. 80% of the [%99mTcO4]− remained in the vial. The ionic liquid was dissolved in the corresponding arene (1 ml). This solution was removed salts and the product was eluted with ethanol.

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Notes and references

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